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Multifocal CNS demyelination after octreotide treatment for metastatic meningioma

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INTRODUCTION

Octreotide (Sandostatin® Novartis, Berne, Switzerland) is a somatostatin analog approved for the treatment of acromegaly and gastrointestinal syndromes of hormone hypersecretion in Switzerland. Since somatostatin receptors (SSTR) are present on most meningiomas, octreotide has been suggested as a salvage treatment for patients with recurrent meningioma with presence of somatostatin receptors confirmed by octreotide SPECT or PET studies(1, 2). We report the case of a patient with metastatic somatostatin receptor-positive meningioma who developed multifocal CNS demyelination after octreotide therapy.

CASE REPORT

The female polyallergic (latex, non-steroidal anti-inflammatory drugs, hayfever, contrast agent) patient was diagnosed with a left sphenoidal meningioma in 1995 at the age of 37. After partial resection the tumor was classified as a WHO grade I meningotheliomatous meningioma and subsequently partially resected again 3 and 7 years later due to progressive growth and subjected to postoperative radiotherapy with 50Gy in June 1999. At the age of 52, a thoracic CT scan carried out for prolonged coughing showed multiple bilateral pulmonary nodules. Histological examination revealed SSTR-positive WHO grade I meningotheliomatous meningioma, compatible with pulmonary metastases. Octreotide scintigraphy of the head revealed positive signalling indicative of positive SSTR status of the primary meningioma. In preparation for planned salvage therapy the patient was subjected to low-dose subcutaneous octreotide treatment, which was given at 0.1 mg three times daily. This was discontinued on treatment day 25 since the patient developed new intermittent bilateral paraesthesia in the L3-L5 dermatomes on day 21 and the patient was admitted to our department. Magnetic resonance imaging (MRI) on day 28 after the first dose revealed

three new periventricular / subcortical and two, presumably new spinal (no previous spinal scan) T2-hyperintense lesions without contrast enhancement or diffusion restriction (Fig. 1). Electrophysiological examinations revealed normal nerve conduction studies of the left sural and tibial nerves, unremarkable visual evoked potentials, but an increased latency of the left tibial nerve on sensory evoked potentials. Cerebrospinal fluid (CSF) analysis during the acute phase and at 6 months follow-up [in brackets] were in accordance with chronic central nervous system (CNS) inflammation: normal cell count (4 [3]/µl), elevated IgG index (1.6 [1.06]; normal: <0.7), positive [positive] CSF oligoclonal bands (OCBs) (serum negative [negative]), elevated CSF/serum index for HSV IgG (5.07 [5.98]), measles IgG [6.62] and CMV IgG (4.06 [4.16]; normal: 1.9), negative HCV and CMV PCR and a partly positive measles/rubella/zoster reaction (elevated CSF anti-measles and rubella IgG titres) (Tab.1).

Cardiovascular examination revealed no signs of atheromatosis of the cranial vessels, an unremarkable serum lipid profile, no history of smoking, no cardiac arrhythmia, but a patent foramen ovale on echocardiography. Anti-CNS (anti-hu, -ri, -yo, -amphiphysin, -cv2, -ta/-ma2, -ma, –recoverin) -antibodies and a vasculitis screening (anti-neutrophil cytoplasmic antibody, rheumatoid factor, MPO, PR3, anti-ß2, anti-cardiolipid, anti-U1-, snRNP-, anti-SS-A/B antibodies) revealed normal results.

Since the discontinuation of octreotide the patient has not reported additional neurological symptoms, but paraesthesia still appear after exposure to heat, e.g. in the sauna. Over the last 2 years, without treatment, the primary cerebral meningioma showed gradual progression, while an additional pulmonary metastase was detected on repeated scans.

DISCUSSION

We report the development of probably autoimmune-mediated multifocal demyelination after octreotide treatment in a patient with metastatic meningioma. The onset of clinical symptoms during treatment as well as MRI and CSF changes are suggestive of an immune process triggered by octreotide administration. In the light of a single clinical event with stable symptoms since the discontinuation of octreotide and negative antibody-screening, a paraneoplastic mechanism seems highly unlikely. Additional investigations showed no indication of an ischaemic, infectious or paraneoplastic etiology of the spinal and cerebral lesions. Sustained polyspecific intrathecal antibody production, elevated IgG index and positive OCBs however suggest a chronic autoimmune reaction as a putative cause for the multifocal cranial and spinal demyelination. The age of onset, unremarkable visual evoked potentials and the timing of onset of symptoms during the administration of octreotide do not exclude alternative demyelinating disorders such as multiple sclerosis (MS) or acute disseminated encephalomyelitis (ADEM), but appear less likely in the given context.

So far no causative relation between octreotide administration and demyelination has been reported, although various possibly similar incidents appear to have occurred in the past. A search of the World Health Organization VigiBase™ pharmacovigilance database (search terms: Sandostatin, Octreotide, demyelination, multiple sclerosis, accessed on Nov 2nd, 2010) revealed 57 cases of paraesthesia, 14 cases of peripheral neuropathy, 6 cases of encephalitis and 1 case of multiple sclerosis relapse in association with octreotide treatment since 1989(3).

Antibody formation against octreotide was shown to occur in 77-81% of intranasally treated individuals within 9 months and in 27% of subcutaneously treated individuals within 3 years(4). Whether such an octreotide-specific immune response can lead to an autoimmune reaction within the CNS, e.g. by cross-reactivity against human autoantigens, is not known.

However, data indicate that somatostatin increases the susceptibility to develop experimental allergic encephalitis (EAE)(5) .

The octreotide doses administered to the patient (0,1mg 3x daily) differed from the dose and schedule originally described as salgave therapy for SSTR positive meningioma (30mg every 28days) (1, 2). It is unclear in how far this might have increased the risk for this putative auto-immune mediated reaction.

Conclusion

This case indicates a possible risk for autoimmune mediated focal demyelination by octreotide treatment in polyallergic patients.

Competing interests

Dr. Schreglmann, Dr. Jelcic & Dr. Taegtmeyer report no competing interests.

Dr. Linnebank receives study grants from Bayer, Biogen, Merck, Novartis, Sanorell, Teva, and honoraria from serving on scientific advisory boards for Bayer, Biogen, Merck, Novartis and Teva.

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Authors` contributions

SRS, IJ and MW collected the data. ML provided help for the interpretation of CSF and imaging results. ABT provided the results of the WHO-database search. SRS prepared

the manuscript, IJ, ABT, ML and MW provided corrections and proof. All authors read and approved the final manuscript.

Patient consent

The patient described in this report has signed a patient consent form for use of her data in research. No pictures of recognizable individuals are being submitted along with this manuscript.

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Figures & Tables

Fig.1: Multifocal demyelination on cerebral and spinal MRI, current intracranial meningioma and pulmonary meningioma metastases:

Arrows highlight sites of demyelination: 4 months before the onset of paraesthesia unaffected tissue is shown in the right temporal, right occipital and left central regions of the brain (A, D, G), showing FLAIR-/T2-hyperintense lesions (without contrast enhancement on T1 or diffusion restriction – data not shown) during the acute episode including cervical and thoracic spinal cord (B, E, H, J, L) and at 4 months follow-up (C, F, I, K, M). The current intracranial meningioma adjacent to the tentorium and cavernous sinus (N) as well as superior orbital fissure (M) and parietal bone (M, N) are indicated by arrows (all courtesy of Prof. B. Schuknecht), as well confirmed bilateral pulmonary meningioma metastases (P, Q, R) (courtesy of Prof. J. Hodler).

Tab. 1: Analysis of cerebrospinal fluid (CSF) during the acute episode and at six months follow-up:

Table 1. Analysis of cerebrospinal fluid (CSF) during the acute episode and at six months follow-up

	Acute episode	6 month follow-up	Normal values
Cell count (cells/µl)	4	3	0-4
CSF/serum index of total IgG	1.6	1.05	<0.7
Oligoclonal bands	positive	positive	negative
CSF/serum index of HSV-specific IgG	5.07	5.98	<1.9
CSF/serum index of CMV-specific IgG	4.06	4.16	<1.9
CSF/serum index of Measles-specific IgG	n.a.	6.62	<1.9
CSF/serum index of Rubella-specific IgG	n.a.	3.2	<1.9
CSF/serum index of VZV-specific IgG	n.a.	0	<1.9
HSV PCR	negative	n.a.	negative
CMV PCR	negative	n.a.	negative